Risk Management Plan

Part VI: Summary of activities in the risk management plan by product

Active substance:	Desmopressin (1-deamino-8-D-arginine vasopressin)
Product(s) concerned (brand name(s)):	MINIRIN, OCTOSTIM, NOCDURNA Ferring's desmopressin products are approved under several different names depending of countries and regions. In this report all Ferring desmopressin products are covered and MINIRIN, OCTOSTIM and NOCDURNA are used to cover all trade names.
MAH/Applicant name:	Ferring Pharmaceuticals A/S Kay Fiskers Plads 11 2300 Copenhagen S Denmark

Data lock point for this module:	30 November 2015
Version number of RMP when this module was last updated:	3.0

VI.1 Elements for summary tables in the European public assessment report (EPAR)

VI.1.1 Summary table of safety concerns

VI.1.1.1 Summary table of safety concerns – Ferring desmopressin products

Summary of safety concerns	
Important identified risks	Hyponatraemia due to water retention, which could be caused also by overdose. Allergic reactions and Hypersensitivity, including anaphylactic reaction
Important potential risks	Thrombotic events
Missing information	Limited data on pregnancy

VI.1.1.2 Summary table of safety concerns – specifically for Nocdurna

Summary of safety concerns	
Important identified risks	Hyponatraemia in elderly patients (≥65 years)
Important potential risks	Precipitation of overt congestive cardiac failure in patients with compensated cardiac insufficiency
Missing information	Long term use in elderly patients

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
Non-interventional Post Authorisation Safety Study with	To describe the risk of hyponatraemia events, as well as	Hyponatraemia in elderly patients (≥ 65 years)	In planning	Final study report planned for 2023

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
NOCDURNA, category 3	cardiovascular and thromboembolic events in patients with nocturia due to nocturnal polyuria treated with NOCDURNA and to collect long term data in elderly patients	Precipitation of overt congestive cardiac failure New occurrence or worsening of existing cardiovascular and thromboembolic events, in nocturia patients treated with NOCDURNA Long term use in elderly patients		

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

VI.1.4 Summary table of Risk Minimisation Measures

VI.1.4.1 Summary table of Risk Minimisation Measures – Ferring desmopressin products

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hyponatraemia due to water retention, which could be caused also by overdose.	Labelling Section 4.3, 4.4, 4.5 and 4.8 The risk of developing hyponatraemia is addressed in the CCDS/SPC in section 4.3 "Contraindications"4.4 "Special warnings and precautions",4.5 "Interaction with other medicinal products and other form of interaction" and in section 4.8 "Undesirable effects". Package leaflet, section 2, 3 and 4	Not applicable
Allergic reactions and Hypersensitivity, including anaphylactic reaction	Labelling section 4.3 "Contraindications"and 4.8 "Undesirable effects".	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Package leaflet: section 2 and 4	
Thrombotic events	None proposed. Potential risk, which is not confirmed by several years of post-marketing experience.	Not applicable
Missing information: Limited data on pregnancy	Labelling section 4.6. Caution required when prescribing to pregnant women is addressed in the CCDS/SmPC in section 4.6 "Pregnancy and Lactation" Package leaflet, section 2	Not applicable

VI.1.4.2 Summary table of Risk Minimisation Measures – specifically for NOCDURNA

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hyponatraemia in elderly patients (≥65 years old)	Labelling Section 4.2, 4.3, 4.4, 4.5 and 4.8 The risk of developing hyponatraemia is addressed in the CCDS/SmPC in section 4.2"Posology and method of administration", 4.3. "Contraindications", 4.4 "Special warnings and precautions", section 4.5 "Interaction with other medicinal products and other forms of interaction" and in section 4.8 "Undesirable effects". Section 4.2: "In elderly patients serum sodium must be within the normal range, before initiating treatment, in the first week (4-8 days after initiation) and again at one month. Nocdurna should be discontinued if the serum sodium level falls below the lower limit of normal range" Package leaflet: section 2 "What	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	you need to know before you take Nocdurna" , section 3 "How to take Nocdurna" and section 4 "Possible side effects"	
Precipitation of overt congestive cardiac failure in patients with compensated cardiac insufficiency	Labelling Section 4.3 The risk of precipitation of overt congestive cardiac failure in patients with compensated cardiac insufficiency is addressed in SmPC section 4.3"Contraindications" Package leaflet: section 2 "What you need to know before you take Nocdurna" , section 3 "How to take Nocdurna" and section 4 "Possible side effects"	Not applicable
Missing information: Long term use in elderly patients	Labelling section 4.2 and 4.4 The risks with desmopressin in elderly patients are addressed in the CCDS/SmPC in section 4.2 Posology and method of administration, Special populations, and in section 4.4 "Special warnings and precautions" Package leaflet: section 2 "What you need to know before you take Nocdurna" , section 3 "How to take Nocdurna" and section 4 "Possible side effects"	Not applicable

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Bedwetting

Bedwetting (also called primary nocturnal enuresis, PNE) is probably the most common developmental sickness in children, affecting 15% to 20% of 5-year-olds. By youth 1% to 2% are affected. In a UK study, 1260 (15.5%) of 7.5 years olds wet the bed; 12% wet "less than once a week" and 0.8% wet "once a week", thus 82.9% of bedwetting children wet "at most once a week".

The pathophysiology of bedwetting is complex, involving neurotransmitters, circadian rhythm (low overnight vasopressin level) and bladder function derangements. Mortality is not expected by bedwetting.

Central Diabetes Insipidus (CDI)

CDI is a fairly uncommon disorder. Epidemiological studies showed prevalence of 20-30 patients per 100,000 inhabitants. It affects all age-groups, and both genders. The yearly incidence rate of new cases of CDI was found to be 3 to 4 patients per 100 000. The incidence of (presumable) congenital CDI was found to be 2 infants per 100 000 infants.

CDI is caused by lack of vasopressin and it could occur due to damage to hypothalamus or the pituitary stalk by tumours, anoxia, encephalitis, radiation, sarcoidosis and histiocytosis. Head trauma has been shown to cause CDI in 15.4% of the cases, and as high as 41% in case of penetrating head trauma.

Mortality is rare in the adults. However, severe dehydration, hypernatraemia, fever, cardiovascular collapse, and death can ensue in children, elderly people, or in those with complicating illnesses.

CDI is primarily treated with desmopressin. Desmopressin dosage is individual in CDI and dosage regimen should then be adjusted in accordance with the patient's response.

Nocturia due to nocturnal polyuria

It is reported that nocturia is the principal clinical manifestation of nocturnal polyuria (NP), in up to 75% of patients seeking treatment for bothersome nocturia. The prevalence of nocturia (and especially when due to NP) increases with age and occurs in both genders.

Nocturnal polyuria has been linked to abnormalities of circadian rhythmic secretion of the endogenous antidiuretic hormone, vasopressin.

Nocturia is the most common reason for sleep disruption, and it can have significant impact in both genders and across all age groups. Nocturia due to NP can have a tangible influence on a person's physical, social and emotional well-being. Several literatures suggest that disruptions in sleep and metabolic/endocrine function are related.

von Willebrands Disease (vWD)

vWD is the most common inherited bleeding disorder estimated to affect 66-100/million in the general population. The symptoms of vWD are excessive skin bleeding, prolonged oozing after surgical procedures as well as excessive bleeding during menstruation in women.

Acquired von Willebrands Disease is a rare bleeding disorder associated with various underlying diseases and with the use of some medication estimated to affect 0.04-0.2% of the general population.

All age groups and both genders are affected. No estimates are available for death of the disease. Prolonged and extensive bleeding in relation to minor injury / surgery or in relation to menstruation and pregnancy is of major concern. Excessive bleeding during menstruation (defined as > 80 mL of blood loss per menstrual cycle) in women with vWD is affecting 74-92% increasing according to severity of vWD.

Haemophilia A

Haemophilia A is estimated to affect 20/100.000 males varying considerably among countries. It is an inherited sickness only affecting boys. Haemophilia affects individuals from all racial/ethnic backgrounds equally.

In a UK study in 6018 haemophiliacs, death in haemophilia (caused by bleeding and its consequences, liver diseases and Hodgkin disease) exceeded death in the general population. Median life expectancy was 63 years for severe haemophilia and 75 years in mild-moderate haemophilia.

Patients with severe haemophilia (clotting factor less than 1% of normal) suffer frequent (20-30 episodes yearly) and spontaneous bleedings (usually in the muscle or joint). Patients with moderate haemophilia have a factor level of 1-5% of normal. Mild haemophilia (factor level of 6-25% of normal) usually precludes bleeding except after injury or surgery. In 1995, out of 1978 haemophiliacs registered 32% were severely affected, 19% moderately and 49% mildly.

Main treatment: Coagulation factor replacement and desmopressin.

Prolonged bleeding time

Unexpected prolonged bleeding in the perioperative phase in a general surgery population is largely attributable to impaired haemostasis including platelet function and plasma coagulation—either inherited or acquired. Approximately 3–5% of patients who undergo elective surgery suffer from impaired haemostasis with a positive medical history of bleeding (approx. 70% primary and drug-induced haemostatic defect and approx. 30% vWD) that is not detected with the routine coagulation screening tests.

All age groups and both genders are affected. Can be congenital, but most cases are acquired due to the (chronic) intake of non-selective, nonsteroidal analgesics that all implies a high risk of bleeding for acute surgical situations.

VI.2.2 Summary of treatment benefits

Primary nocturnal enuresis (PNE), central diabetes insipidus (CDI), renal concentration capacity testing and haematological indications

For several decades desmopressin has been used for treatment of PNE and CDI and later expanded to use for renal concentration capacity testing, and haematological indications. Ferring has not performed a clinical development program in these indications. The benefit of desmopressin in these indications is supported by the long clinical experience and data published in international medical and scientific literature.

Nocturia associated with nocturnal polyuria

Three clinical trials (NOCT-2-A (males), NOCT-3-A (females), and NOCT-4 (both genders)) provided the first efficacy data for desmopressin in the treatment of nocturia associated with nocturnal polyuria. For 3-weeks, patients received either placebo (a dummy treatment) or desmopressin tablets. The number of participants in [NOCT-2-A], [NOCT-3-A], and [NOCT-4] were 146, 142, and 126 respectively. The primary efficacy endpoint was the percent of patients with a 50% reduction in the number of nocturnal voids/night. In each trial, significantly more patients on desmopressin than placebo achieved this endpoint The primary efficacy endpoint was analysed separately for patients below and above the age of 65 years and the effect of desmopressin was similar in the two age groups.

The efficacy of NOCDURNA has been demonstrated in two randomised double blinded placebo controlled trials in respectively 268 women (CS40, desmopressin Melt 25 microgram versus placebo) and 395 men (CS41, desmopressin Melt 50 microgram and 75 microgram versus placebo) with nocturia.

The co-primary endpoints , measured from baseline to final visit in 3 months, were change in the mean number of nocturnal voids and proportion of subjects with >33% decrease in the mean number of nocturnal voids.
Both trials met the 2 co-primary endpoints with statistically significant differences favouring desmopressin Melt over the 3-month period. There was a statistically significant decrease in nocturnal voids with desmopressin Melt (-1.46) compared to placebo (-1.24) in the female study (p=0.028) and with desmopressin Melt 50 microgram (-1.25) compared to placebo (-0.88) in the male study (p=0.0003). The proportion of subjects with >33% decrease in nocturnal voids was significantly higher with desmopressin Melt. There was a statistically significant improvement in the first undisturbed sleep period/time to first void and in quality of life in the patients treated with desmopressin Melt in both trials.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

VI.2.4.1 Summary of safety concerns – Ferring desmopressin products

Important identified risks

Risk	What is known	Preventability
Hyponatraemia due to water retention, which could be caused also by overdose.	Decreased blood sodium concentration is a common side-effect and approximately one in 100 people treated with desmopressin may experience it. Decreased blood sodium concentration may cause headache, nausea, vomiting, weight increase, discomfort, stomach pain, muscle cramps, dizziness, confusion, decreased consciousness and in severe cases convulsions and coma. However, symptoms may resolve completely without any treatment	It can be avoided by following the precautions in the labelling, including limit the fluid intake, as well as the contraindications and information concerning interaction with other medicinal products. MINIRIN tablet and Melt *Nocturia indication – elderly patients* The initiation of treatment in patients > 65 years is not recommended. Should physicians decide to initiate desmopressin treatment in these patients then serum sodium should be measured before beginning the treatment and 3 days after initiation or increase in dosage and at other times during treatment as deemed necessary by the treating physician.
Allergic reactions and Hypersensitivity, including anaphylactic reaction	Allergic reactions and hypersensitivity, including anaphylactic reactions, can in rare cases be fatal if adequate medical treatment is not provided. Medication-triggered anaphylaxis/anaphylactic reaction can occur in patients of any age; however middle-aged and elderly are particularly susceptible, primarily due to concomitant diseases such as COPD and cardiovascular disease.	Addressed in section 4.3 and 4.8: Use in patients with hypersensitivity to the active substances or to any of the excipients is contraindicated

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Blood clots (thrombotic/embolic events)	The potential risk of developing blood clots is due to the effect of high doses of desmopressin that may cause clotting after release of coagulation factors in the blood of patients with other risk factors. Blood clots is a very rare side-effect and post-approval data showed approximately one in one million people treated with desmopressin may experience it. Symptoms of blood clots are depending on their size and location, may include leg pain, swelling or redness or sudden-onset shortness of breath, chest pain, abnormal heart beats and may be complicated by collapse, shock and heart attack. Disorders of blood coagulation, immobility, oral contraceptives, smoking and injury to blood vessel walls are among the recognised risk factors.

Missing information

Risk	What is known
Limited data on pregnancy	There is limited information on use of desmopressin in pregnant women, mainly in patients with central diabetes insipidus and coagulation disorders. According to the product labels caution should be exercised when prescribing desmopressin to pregnant women and as with all medication used during pregnancy, the physician should weigh possible therapeutic advantages against potential risks in each case.

VI.2.4.2 Summary of safety concerns – NOCDURNA

Important identified risks

Risk	What is known	Preventability
Hyponatraemia in elderly patients (≥65 years old)	Decreased blood sodium concentration is a common side-effect and approximately one in 100 people treated with desmopressin may experience it. Decreased blood sodium concentration may cause headache, nausea, vomiting, weight increase, discomfort, stomach pain, muscle cramps, dizziness, confusion, decreased consciousness and in severe cases convulsions and coma. However, symptoms may resolve completely without any treatment	In elderly patients serum sodium must be within the normal range, before initiating treatment, in the first week (4-8 days after initiation) and again at one month. NOCDURNA should be discontinued if the serum sodium level falls below the lower limit of normal range.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Worsening of existing heart failure in patients with compensated cardiac insufficiency (precipitation of overt congestive cardiac failure in patients with compensated cardiac insufficiency)	Heart failure is a disorder in which the heart pumps blood inadequately, leading to reduced blood flow. The body has several mechanisms to compensate for heart failure, however eventually these may further weaken the heart and result in back-up (congestion) of blood in the veins and lungs. Heart failure is a prevalent disease affecting over 5.1 million people in the United States and over 23 million people worldwide. Risk factors for developing heart failure include increased weight, diabetes, smoking, increased blood pressure, chronic lung disease (chronic obstructive pulmonary disease). Patients with heart failure accumulate water in the body. These patients may present with increased urine production at night (nocturnal polyuria) because the accumulated water returns from peripheral body parts (especially the legs) to the blood system when the patient lays down. Desmopressin shall not be used in this patient group due to the risk of worsening of water accumulation in the body and increased risk of hyponatraemia (hyponatraemia is described above).

Missing information

Risk	What is known
Long term use in elderly patients	Approximately half of the patients who participated in the clinical trials with desmopressin in nocturia were 65 years old or older. The duration of treatment with desmopressin for the majority of the patients in the clinical trials was 6 months or less.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development planStudy/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Non-interventional Post Authorisation Safety Study (PASS) with NOCDURNA, category 3	To describe the risk of hyponatraemia events, as well as cardiovascular and thromboembolic events in patients with nocturia due to nocturnal polyuria treated with NOCDURNA and to collect long term data in elderly patients	Hyponatraemia in elderly patients (≥65 years) Precipitation of overt congestive cardiac failure. New occurrence or worsening of existing cardiovascular and thromboembolic events in nocturia patients treated with NOCDURNA. Long term use in elderly patients	In planning phase	Final study report expected 2023

Studies which are a condition of the marketing authorisation

Non-interventional Post Authorisation Safety Study (PASS) with NOCDURNA, category 3 (see above).

VI.2.7 Summary of changes to the Risk Management Plan over time

Table 1: Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
3.0	23/02/2016	Risks specifically for NOCDURNA: Important Identified risk: "Hyponatraemia in elderly patients (⩾65 years)" Important potential risk: "Precipitation of overt congestive cardiac failure in patients with compensated cardiac insufficiency" Missing information was revised to: "Long term use in elderly patients"	The safety concerns were updated in alignment with the recommendations received during EU decentralised procedure for NOCDURNA SE/H/1507/01-02/DC in 2016. Long term use in patients with renal insufficiency" Was removed as "Missing information" following the recommendations above.
2.0	16/12/2015	"Anaphylactic reaction (including allergic reactions due to fish gelatine in melt formulation)" was removed as a potential risk and "Allergic reactions and Hypersensitivity, including anaphylactic reaction" was added as an important identified risk. The term of the important identified risk of "Hyponatraemia" was revised. As proposed by PRAC wording of "Overdose, leading to water retention and hyponatremia" may inappropriately link hyponatraemia only to overdose, so to address the conditions where hyponatraemia may occur without overdose of desmopressin, the risk of "Hyponatraemia" was revised to "Hyponatraemia due to	The safety concerns were updated in alignment with the recommendations from the PSUR assessment in 2015 (PSUSA/00000964/201412, EMA/PRAC/589834/2015), and with recommendations received during EU decentralised procedure for NOCDURNA (SE/H/1507/01-02/DC) in 2015

Version	Date	Safety Concerns	Comment
		water retention, which could be caused also by overdose". Specifically for OCDURNA: Especially in the elderly patients (≥65 years old), serum sodium concentrations below normal range and with concomitant diuretic use. An important potential risk was added specifically for NOCDURNA: "Precipitation of overt congestive cardiac failure in patients with compensated cardiac insufficiency" Missing information: "Limited data on pregnancy" and "Specifically for NOCDURNA: "Long term use in the elderly and patients with renal insufficiency" were added	
1.0	23/03/2015	Important identified risk: "Hyponatraemia" Important potential risks: "Thrombosis" "Anaphylactic reaction (including allergic reactions due to fish gelatine in melt formulation)" Missing information: None	